COMBINED DECLARATION
AND POWER OF ATTORNEY

Attorney Docket No.
28200-C1

As a below named joint inventor, each of us hereby declares as follows:

My residence, post office address and citizenship are as stated below next to my name.

I believe that I am an original, first, and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled:

2-(2-AMINO-1,6-DIHYDRO-6-OXO-PURIN-9-YL)METHOXY-1,3-PROPANEDIOL DERIVATIVE

the specification of which was filed in the U.S. Patent & Trademark Office on May 30, 1995 as Application No. 08/453,223.

I state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I acknowledge the duty to disclose information of which I am aware that is material to the examination of this application in accordance with 37 CFR 1.56(a).

I claim the benefit under 35 U.S.C. 120 of copending U.S. Patent Application No. 08/281,893, filed July 28, 1994, and, insofar as the subject matter of the claims is not disclosed in that prior application in the manner provided by 35 U.S.C. 112, ¶1, I acknowledge the duty to disclose material information as defined in 37 CFR 1.56(a) that occurred between the filing date of that prior application and the filing date of this application.

I hereby appoint the following attorneys to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith:

Y. P. Chow, Registration No. 30,740
John A. Dhuey, Registration No. 26,265
Derek P. Freyberg, Registration No. 29,250
Alan M. Krubiner, Registration No. 26,289
Walter Kurz, Registration No. 37,373
William Schmonsees, Registration No. 31,796
Herwig von Morzé, Registration No. 29,484

Address all written correspondence to:

Heller Ehrman White & McAuliffe
525 University Avenue
Palo Alto, California 94301-1900.

COMBINED DECLARATION
AND POWER OF ATTORNEY

Attorney Docket No.
28200-C1

Direct all telephone calls to:

Derek P. Freyberg, at (415) 324-7014.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

FIRST JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
John J. Nestor, Jr.		2/4/97
RESIDENCE		CITIZENSHIP
Louisville, Kentucky		U.S.A.
POST OFFICE ADDRESS		
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SECOND JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
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THIRD JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
Hans Maag		2/10/97
RESIDENCE		CITIZENSHIP
Menlo Park, California		U.S.A. and Switzerland
POST OFFICE ADDRESS		
745 Stanford Avenue, Menlo Park, California 94025		

COMBINED DECLARATION AND POWER OF ATTORNEY

Attorney Docket No. 20200-C3

As a below named joint inventor, each of us hereby declares as follows:

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2-(2-AMINO-1,6-DIHYDRO-6-OXO-PURIN-9-YL)METHOXY-1,3-PROPANEDIOL DERIVATIVE

the specification of which was filed with the Patent & Trademark Office on March 4, 1997 as Application No. 08/812,991.

I state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I acknowledge the duty to disclose information of which I am aware that is material to the examination of this application in accordance with 37 CFR 1.56(a).

I hereby appoint the following attorneys to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith:

William B. Anderson, Reg. No. 41,585
Y. Ping Chow, Registration No. 30,740
Robert F. Dennis, Reg. No. 40,988
Jacques M. Dulin, Reg. No. 24,067
Derek P. Freyberg, Registration No. 29,250
Walter Kurz, Registration No. 37,373
Edward J. Lynch, Reg. No. 24,422
Priscilla H. Mark, Reg. No. 41,970
William Schmonsees, Registration No. 31,796
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COMBINED DECLARATION
AND POWER OF ATTORNEY

Attorney Docket No.
28200-C3

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FIRST JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
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COMBINED DECLARATION AND POWER OF ATTORNEY

Attorney Docket No. 28200-C3

THIRD JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
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FOURTH JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
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FIFTH JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
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COMBINED DECLARATION
AND POWER OF ATTORNEY

Attorney Docket No.
28200-C3

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Robert F. Dennis, Reg. No. 40,988
Jacques M. Dulin, Reg. No. 24,067
Derek P. Freyberg, Registration No. 29,250
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Edward J. Lynch, Reg. No. 24,422
Priscilla H. Mark, Reg. No. 41,970
William Schmonsees, Registration No. 31,796
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COMBINED DECLARATION
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Palo Alto, California 94301-1908.

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Derek P. Freyberg, at (650) 324-7014.

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FIRST JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
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COMBINED DECLARATION
AND POWER OF ATTORNEY

Attorney Docket No.
28200-C3

THIRD JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
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Menlo Park, California	U.S.A. and Switzerland

POST OFFICE ADDRESS

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FOURTH JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
Charles A. Dvorak	Charles A. Dvorak	10/14/99

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FIFTH JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
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RESIDENCE	CITIZENSHIP
San Francisco, California	U.S.A.

POST OFFICE ADDRESS

921 Minnesota Street, San Francisco, California

PATENTS
Attorney Docket No. 28200-C1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

John J. Nestor et al. :

App. No.: 08/453,223 : Art Unit: 1611

Filed: May 30, 1995 : Examiner: Mark L. Berch

For: 2-(2-AMINO-1,6-DIHYDRO-6-OXO-PURIN-9-YL)METHOXY-1,3-PROPANEDIOL DERIVATIVE

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

DECLARATION OF SUSAN MALCOLM

I, Susan L Malcolm, declare as follows:

1. I was awarded the degree of B.Sc. in Chemistry by the Univerity of Manchester Institute of Science and Technology in 1971. My career since then has been entirely in the pharmaceutical industry. I have been working in Research at Roche Products Ltd for 26 years and all of that time in the field of drug metabolism and pharmacokinetics. My experience covers development and use of analytical methods for new drugs in biological fluids as well as the design and implementation of all studies needed for pre-clinical aspects of drug registration using both in-vivo and in-vitro techniques. My present position at Roche is as a pre-clinical science leader where my responsibilities is to ensure that all aspects of pre-clinical science, drug metabolism and pharmacokinetics, safety and formulation, are addressed and evaluated in the selection of drug candidates and to ensure that all pre-clinical aspects of drug metabolism and pharmacokinetics are comprehensively evaluated during the development phase of a new drug.

2. I was the Sponsor Study Director on a study performed for Roche Products Limited on the bioavailability of oral doses of ganciclovir, ganciclovir monovalinate (as the hydrochloride salt), ganciclovir bisvalinate (as the hydrochloride salt), acyclovir, and acyclovir valinate [valacyclovir] (as the hydrochloride salt), in the rat.

3. Briefly, the study involved the oral dosing of a number of rats with the various test compounds, at a dose equivalent to 10 mg/kg of ganciclovir or acyclovir (as appropriate to the compound tested), and taking plasma samples at nine fixed times (15 and 30 minutes, 1, 2, 3, 5, 7, 10, and 24 hours), after the dosing. Four rats were used per compound tested per sample time. The plasma samples were analyzed for their concentration of ganciclovir or acyclovir (as appropriate to the compound tested). From these concentration measurements, the area under the plasma concentration versus time curve [AUC], a measure of the total systemic exposure after the oral dose, was calculated for each test compound.

4. Intravenous doses of both ganciclovir and acyclovir were also given at 10mg/kg to a number of rats. Following these doses samples were taken at the same times as above plus at the earlier time of 5 minutes. This sample was added because of the immediate high concentrations following a bolus iv dose and the rapid fall as the compounds are distributed throughout the body. The plasma concentrations were measured in the same way as the oral dose and the area under the plasma time curve following the intravenous dose calculated which gives a measure of the maximum systemic exposure of the test compound, the whole dose being delivered into the blood.

5. The absolute bioavailability of the orally dosed compounds was calculated by dividing the AUC for the orally dosed compound by the AUC for the intravenously dosed ganciclovir or acyclovir (as appropriate), and expressing the result as a percentage.

6. The foregoing methods are standard methods used to determine the oral bioavailability of compounds.

7. The results of the study are as follows:

Compound Tested (Oral)	Bioavailability, % (±SD)
ganciclovir	6.9 (0.76)
ganciclovir bisvalinate hydrochloride	34.0 (2.37)
ganciclovir monovalinate hydrochloride	55.4 (4.41)
acyclovir	14.2 (0.53)
valacyclovir hydrochloride	53.4 (9.40)

8. These results demonstrate that the bioavailability of orally administered ganciclovir monovalinate is about 1.6 times greater than the bioavailability of orally administered ganciclovir bisvalinate and is about 8 times greater than the bioavailability of orally administered ganciclovir itself. By comparison, although the bioavailability of orally administered acyclovir is about 2.1 times greater than that of orally administered ganciclovir, the bioavailability of orally administered valacyclovir is only about 3.8 times that of orally administered acyclovir, and is less than the bioavailability of orally administered ganciclovir monovalinate.

9. I consider it likely that the lower biovailabilities for each of the ganciclovir compounds tested in this study when compared to the data reported in the specification of the application [the bioavailabilities for acyclovir and valacyclovir hydrochloride being somewhat lower than those of **Beauchamp et al.** but generally more comparable] result from a difference in procedure between the present study and that reported previously. Analysis of the data sets show that the differences lie in the calculated value for the AUC for the intravenous dose of ganciclovir and specifically at the early sampling times, 5 and 15 minutes. At these times drug levels are falling rapidly and small differences between theoretical and actual times can alter the concentration markedly. Also the high concentrations present makes a significant contribution to the calculation of the AUC, therefore concentration differences are reflected by marked AUC differences. In the present study particular care was taken in the timing of these samples and the lower standard deviation on the results suggest a greater sampling accuracy.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that this declaration was executed by me on September 3, 1998 at Welwyn Garden City, Hertforshire, England.

Susan Malcolm

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